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Low doses of fludrocortisone and hydrocortisone, alone or in combination, on vascular responsiveness to phenylephrine in healthy volunteers

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Physiologic doses of a combination of hydrocortisone and fludrocortisone have been shown to improve the prognosis of patients with vasopressor-unresponsive septic shock, especially of those with relative adrenal insufficiency.
- A single administration of hydrocortisone has been shown to enhance the pressor response to phenylephrine in healthy volunteers and to norepinephrine in septic shock patients. Similar data do not exist for fludrocortisone.
- The need for dual glucocorticoid (hydrocortisone) and mineralocorticoid (fludrocortisone) supplementation in septic shock is currently debated.

WHAT THIS STUDY ADDS

- Single administrations of fludrocortisone and hydrocortisone decrease the pressor response to phenylephrine in healthy volunteers with hypo-aldosteronism.
- These similar effects of hydrocortisone and fludrocortisone probably express a rapid non-genomic vasodilating effect of the two steroids in the context of acute volume loading.

AIMS

A single administration of hydrocortisone has been shown to enhance the pressor response to phenylephrine in healthy volunteers and to norepinephrine in septic shock patients. Similar data do not exist for fludrocortisone. Since there continues to be disagreement about the utility of fludrocortisone in septic shock, we assessed the effects of a single administration of low doses of hydrocortisone (50 mg intravenously) and fludrocortisone (50 µg orally), given either alone or in combination, on phenylephrine mean arterial pressure and cardiac systolic and diastolic function dose–response relationships in 12 healthy male volunteers with hypo-aldosteronism induced by intravenous sodium loading.

METHODS

This was a placebo-controlled, randomized, double-blind, crossover study performed according to a 2 × 2 factorial design. Subjects received first a 2000 ml infusion of NaCl 0.9% during 2 h. Then fludrocortisone 50 µg (or its placebo) was administered orally and hydrocortisone 50 mg (or its placebo) was injected intravenously. At 1.5 h after treatment administration, incremental doses of phenylephrine were infused (from 0.01 to 3 µg kg^{-1} min^{-1}), each dose being infused during 5 min.

RESULTS

Both fludrocortisone ($P < 0.001$) and hydrocortisone ($P = 0.002$) induced a significant decrease in pressor response to phenylephrine, their effects being additive (fludrocortisone × hydrocortisone interaction, $P = 0.792$). The two drugs did not induce any detectable cardiac effect.

CONCLUSIONS

Single administrations of fludrocortisone and hydrocortisone decreased the pressor response to phenylephrine in healthy volunteers with hypo-aldosteronism. These similar effects of hydrocortisone and fludrocortisone probably express a rapid non-genomic vasodilating effect of the two steroids in the context of acute volume loading.

Introduction

Physiologic doses of a combination of hydrocortisone (HC) and fludrocortisone (FC) have been shown to improve prognosis in patients with catecholamine-resistant septic shock, especially in those with relative adrenal insufficiency [1–3]. These favourable effects could result from anti-inflammatory and vascular actions which involve genomic and non-genomic mechanisms [4]. Low doses of HC (glucocorticoid) have been shown to improve rapidly (1 h after treatment administration) vascular responsiveness to catecholamines in septic shock patients and in healthy volunteers [5, 6]. In contrast, similar effects have never been reported for FC (mineralocorticoid). Furthermore, favourable effects were not found when HC was given alone in less severe septic shock [7] and when FC was given as an add-on drug in septic shock treated with HC [8]. Therefore there is a debate on the need for dual glucocorticoid and mineralocorticoid supplementation in septic shock, i.e. as to whether FC should be added to HC [9, 10]. Since hydrocortisone has dual intrinsic mineralocorticoid and glucocorticoid activity, current clinical guidelines propose that fludrocortisone (50 µg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity and is optional if hydrocortisone is used [9].

FC is an old synthetic analogue of aldosterone. FC and aldosterone have been shown to enhance intracellular calcium in rat and rabbit aortic vascular smooth muscle cells in the minutes following their administration [11], and FC has shown rapid and transient inotropic action on cat isolated cardiac tissue [12]. Aldosterone has also been able to decrease rapidly forearm blood flow in healthy volunteers reflecting a non-genomic contraction of resistances arteries [13]. These observations suggest that FC could display similar effects to HC on vascular contractility.

We have recently reported the biological and haemodynamic effects of low doses of FC and HC, alone or in combination, in a model of hypo-aldosteronism in healthy volunteers [14]. During this study, we also assessed the dose–pressor response relationship to phenylephrine (PE) 1.5 h after treatments administration. This paper reports the methodology and results of this specific part of the study.

Methods

The study was approved by our regional committee for the protection of people in biomedical research (Comité de Protection des Personnes de Rennes Ouest V) on March 5 2008 (n°08/08–667) and by the French competent authority (AFSSaPS: Agence Française de Sécurité Sanitaire des Produits de Santé) on March 17 2008 (n°A80097-57). The study was also registered in the EudraCT data base (n°2007–007969-20). All subjects gave written informed consent to participate.

Subjects

Twelve healthy male volunteers, aged 24 ± 3 years, with a body mass index of 23.0 ± 1.9 kg m^{-2} were included. Subjects had to be non-smokers and medication-free. Before enrolment, they underwent clinical examination, 12-lead electrocardiogram, trans-thoracic echocardiography, drug screening in urine and routine biological tests.

Protocol

The study protocol has already been reported in details [14]. Briefly, this was a placebo-controlled, randomized, double-blind, crossover, four period study performed according to a 2 × 2 factorial design. Each period was separated from the next one by a washout interval of at least 14 days. Subjects received in a random order FC placebo + HC placebo, FC + HC placebo, FC placebo + HC or FC + HC. FC (50 µg) was administered orally and HC sodium hemisuccinate (50 mg) was injected intravenously as a bolus. Drugs doses and routes of administration were those used in septic shock patients [1, 7, 8]. All experiments were conducted in a quiet and temperature controlled (at 20 ± 2°C) room.

All study periods were identical. Subjects arrived at the clinical investigation unit of the Inserm 0203 Clinical Investigation Centre of Rennes University Hospital at 06.45 h after an overnight fast and they were immediately placed in the supine position. At 07.30 h, an indwelling catheter with a heparinized lock was inserted into a forearm vein of the left arm for blood sampling. At 07.45 h, another catheter was inserted into a forearm vein of the right arm to allow i.v. infusion of 2000 ml of NaCl 0.9% during 2 h. Such an acute volume expansion has previously been shown to induce significant decrease of plasma renin activity and aldosterone in healthy males [15]. At 08.00 h, they had a standardized breakfast. At the end of the NaCl 0.9% infusion, baseline biological and haemodynamic measures were performed, followed by treatment administration. The same measures were repeated 1 h after treatment administration. Thirty min later (i.e. 1.5 h after treatment administration), PE was infused in a stepwise manner (each dose being maintained for 5 min) at 0, 0.05, 0.1, 0.25, 0.5, 0.75, 1, 1.5, 3, 6, 9 and 12 µg kg^{-1} min^{-1}. At each dose, blood pressure and heart rate were measured within the last minute of infusion. At doses of 0, 0.1, 1 and 3 µg kg^{-1} min^{-1}, a complete echocardiographic investigation was also performed which allowed the assessment of systolic and diastolic function as well as filling pressures.

Haemodynamic variables

Systolic, diastolic and mean blood pressures and heart rate were recorded non-invasively in the supine position, at

rest, using a brachial sphygmomanometer (Dynamap ProCare, GE Healthcare, Freiburg, Germany). At each dose, the values reported for systolic, diastolic and mean blood pressures and heart rate were the means of three measurements. For each volunteer, all measures were taken with the same sphygmomanometer.

Echocardiographic variables

Echocardiography was performed using a ViVid Q (GE Healthcare, Horten, Norway). At every step, loops of three heart beats (with ECG tracing) were saved considering the parasternal long axis view, the parasternal short axis view centred on the papillary muscle and the apical 4, 2 and 3 chambers views. The frame rate was 70 Hz. Images were recorded with a dedicated attention to get the best border delineation of the epi- and endo-cardial left ventricular (LV) walls. Pulse Doppler was also recorded as well as pulse tissue Doppler. Each examination was digitally recorded for treatment afterwards on the dedicated EchoPAc workstation with the Q-analysis capability (GE Healthcare, Horten, Norway). The following variables were drawn from this analysis: LV end-systolic volume, LV end-diastolic volume, stroke volume and cardiac output. LV systolic function was assessed considering each component of LV deformation in systole (longitudinal shortening, radial thickening and circumferential shortening) [16]. Right ventricular (RV) systolic function was assessed using the longitudinal strain and tissue Doppler recorded at the tricuspid annulus. Diastolic function was assessed using left atrial size, mitral inflow and pulse tissue Doppler according to guidelines [17]. Arterial and end-systolic elastances were calculated as follows: arterial elastance = 0.9 × systolic blood pressure/stroke volume; end-systolic elastance = 0.9 × systolic blood pressure/end-systolic volume [18].

Statistical analysis

Statistical analysis was performed using SAS statistical software V9.1 (SAS Institute, Cary, NC, USA). Results are expressed as means ± SD in text and tables and as means ± SEM in figures for clarity. Vascular and cardiac responses to PE were analyzed using a four way ANOVA (subject, PE dose, FC, HC) with three second and one third order interactions. All analyses were performed according to the 2 × 2 factorial design. The FC effect compared the two periods where subjects received FC (FC alone or FC + HC) with the two periods where they did not (HC alone or placebo). The HC effect compared the two periods where subjects received HC (HC alone or FC + HC) with the two periods where they did not (FC alone or placebo). FC × HC interaction assessed whether the effects of the two treatments were additive (non significant interaction) or not (significant interaction). For all analyses, P values < 0.05 were considered significant.

Results

Aldosterone and plasma renin concentrations decreased after acute NaCl 0.9% infusion from 67.8 ± 34.7 to 25.2 ± 8.1 pg ml^{-1} and from 10.1 ± 6.0 to 6.0 ± 2.7 pg ml^{-1}, respectively, reflecting the hypo-aldosteronism induced by sodium loading.

Basal values and effects 1 h after treatment administration

There were no significant differences, at baseline and 1 h after treatment administration, in any of the biological and haemodynamic variables between the four periods of investigation [14].

Systemic haemodynamic response to PE

Blood pressure and heart rate Among the 12 doses of PE planned in the protocol, only the first nine could be administered. Indeed, several volunteers began to feel sick with sweating and bradycardia below 35 beats min^{-1} at 3 µg kg^{-1} min^{-1} and greater doses could not be infused. For one volunteer, the dose of 1 µg kg^{-1} min^{-1} could not be administered during one of the four periods of investigation for the same reasons.

Figure 1 shows the effect of the stepwise infusion of PE on mean blood pressure (Figure 1A) and heart rate (Figure 1B).

PE increased mean blood pressure in a dose-dependent manner (dose effect, $P < 0.001$). A significant decrease in the pressor response to PE was induced by FC ($P < 0.001$) and HC ($P = 0.002$), the two drugs showing additive effects (FC × HC interaction, $P = 0.792$). The maximum observed increase in mean blood pressure was 55 ± 18 mmHg after placebo, 51 ± 14 mmHg after FC alone, 43 ± 13 mmHg after HC alone and 42 ± 16 mmHg after FC + HC.

PE decreased heart rate in a dose-dependent manner (dose effect, $P < 0.001$) but there was no significant effect of FC and HC. The maximum observed decrease in heart rate was −19 ± 11 beats min^{-1} after placebo, −19 ± 10 beats min^{-1} after FC alone, −22 ± 10 beats min^{-1} after HC alone and −24 ± 11 beats min^{-1} after FC + HC.

Cardiac output and systemic vascular resistance Figure 2 shows the effect of the stepwise infusion of PE on cardiac output (Figure 2A) and systemic vascular resistance (Figure 2B). PE decreased cardiac output and increased systemic vascular resistance in a dose-dependent manner (dose effect, $P < 0.001$ for both) but there was no significant effect of FC and HC on these two variables.

Cardiac response to PE

Table 1 shows the effect of the stepwise infusion of PE on echocardiographic variables. PE decreased mitral E-wave deceleration time (dose effect, $P = 0.019$) and increased

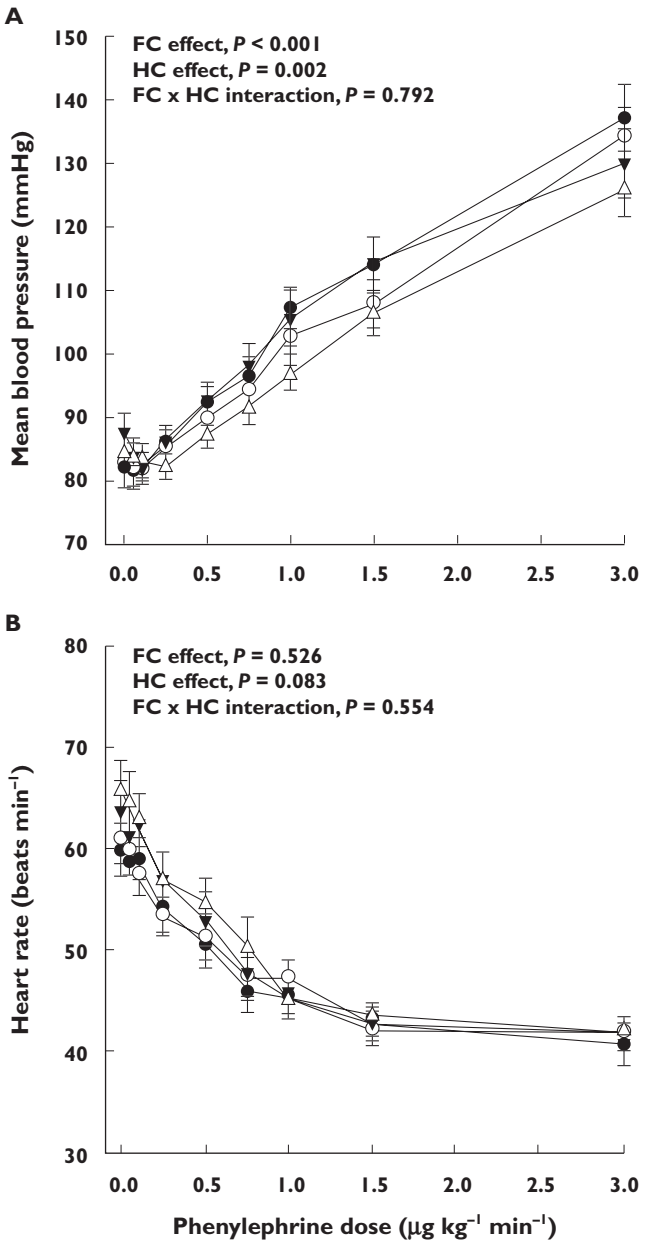

Figure 1

Variations of mean blood pressure (A) and heart rate (B) induced by stepwise infusion of phenylephrine. Data are mean ± SEM; ○ FC, fludrocortisone; ▼HC, hydrocortisone. ● placebo; △ FC + HC

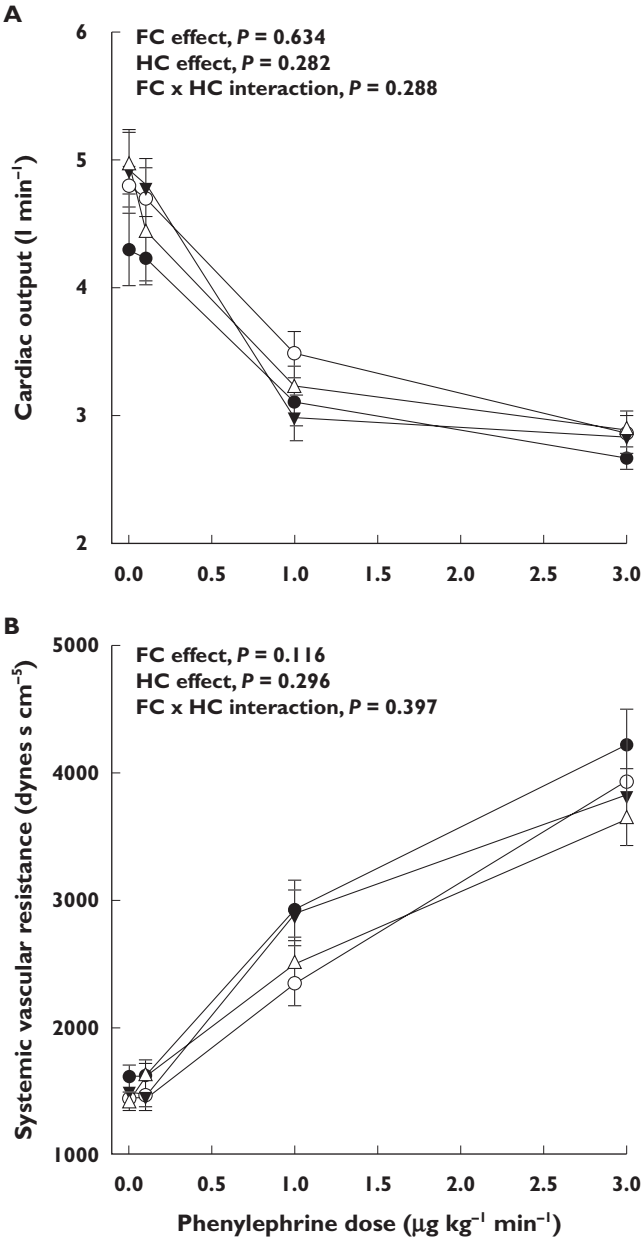

Figure 2

Variations of cardiac output (A) and systemic vascular resistances (B) induced by stepwise infusion of phenylephrine. Data are mean ± SEM; ○ FC, fludrocortisone; ▼HC, hydrocortisone; ● placebo; △ FC + HC

E/e′ ratio (dose effect, $P < 0.001$) in a dose-dependent manner but there was no significant effect of FC and HC on these two variables. Moreover, there was no significant effect of FC and HC on LV and RV systolic and diastolic functions.

Arterial and end-systolic elastance modifications induced by PE

Figure 3 shows the effect of the stepwise infusion of PE on arterial (Figure 3A) and end-systolic elastances (Figure 3B). PE increased arterial and end-systolic elastances in a dose-dependent manner (dose effect, $P < 0.001$ for both). A significant decrease of arterial elastance was induced by HC ($P = 0.019$) and a similar tendency was observed for FC ($P = 0.058$). The maximum observed increase of arterial elastance was 1.2 ± 0.6 mmHg ml^{-1} after placebo, 0.9 ± 0.4 mmHg ml^{-1} after FC alone, 1.0 ± 0.5 mmHg ml^{-1} after HC alone and 0.9 ± 0.5 mmHg ml^{-1} after FC + HC. There was no significant effect of FC and HC on end-systolic elastance.

Table 1

Echocardiographic monitoring of systolic and diastolic functions during stepwise infusion of phenylephrine

Variable	PE dose (μg kg^{-1} min^{-1})	Placebo	FC	HC	FC + HC	*P* values PE effect	FC effect	HC effect	FC × HC inter-action
LV end-systolic volume (ml)	0	43 ± 13	46 ± 11	48 ± 9	43 ± 6	0.426	0.469	0.143	0.182
	0.1	47 ± 12	46 ± 14	47 ± 17	43 ± 11				
	1	48 ± 12	50 ± 11	49 ± 9	45 ± 11				
	3	49 ± 13	48 ± 10	47 ± 13	45 ± 10				
LV end-diastolic volume (ml)	0	122 ± 24	123 ± 24	126 ± 20	119 ± 17	0.322	0.479	0.854	0.701
	0.1	117 ± 23	123 ± 23	120 ± 22	121 ± 17				
	1	116 ± 26	119 ± 24	124 ± 23	118 ± 23				
	3	118 ± 29	120 ± 17	113 ± 16	115 ± 18				
Stroke volume (ml)	0	79 ± 14	77 ± 14	78 ± 16	76 ± 16	0.059	0.100	0.072	0.860
	0.1	70 ± 18	78 ± 14	73 ± 10	77 ± 12				
	1	69 ± 16	69 ± 15	74 ± 19	73 ± 19				
	3	69 ± 19	71 ± 12	67 ± 12	70 ± 13				
LV longitudinal global strain (%)	0	−18.8 ± 3.8	−18.4 ± 2.5	−18.5 ± 4.0	−19.0 ± 3.8	0.116	0.525	0.695	0.607
	0.1	−17.7 ± 3.8	−19.0 ± 1.6	−19.3 ± 4.1	−19.5 ± 3.6				
	1	−16.6 ± 4.7	−18.3 ± 4.8	−15.9 ± 3.7	−18.7 ± 4.5				
	3	−18.6 ± 5.3	−15.7 ± 5.5	−17.0 ± 4.1	−17.2 ± 4.9				
LV radial global strain (%)	0	51.1 ± 10.4	49.4 ± 9.9	46.1 ± 17.2	51.1 ± 14.8	0.278	0.903	0.810	0.180
	0.1	50.6 ± 18.5	46.3 ± 10.7	41.9 ± 12.2	47.3 ± 11.8				
	1	45.2 ± 14.4	37.4 ± 15.6	43.8 ± 7.8	41.9 ± 13.8				
	3	46.1 ± 12.0	48.8 ± 16.1	42.6 ± 11.6	48.0 ± 10.3				
LV circumferential global strain (%)	0	−19.7 ± 5.7	−19.9 ± 2.9	−19.2 ± 2.9	−19.3 ± 4.1	0.584	0.145	0.100	0.232
	0.1	−17.6 ± 3.6	−18.3 ± 3.5	−19.3 ± 4.8	−19.3 ± 5.0				
	1	−17.4 ± 1.8	−19.9 ± 2.6	−20.2 ± 3.5	−19.1 ± 3.9				
	3	−17.5 ± 2.7	−19.2 ± 3.8	−18.7 ± 4.9	−18.8 ± 2.9				
RV longitudinal global strain (%)	0	−25.5 ± 4.3	−24.9 ± 3.5	−26.8 ± 4.9	−26.5 ± 9.9	0.639	0.314	0.526	0.029
	0.1	−24.4 ± 5.5	−28.0 ± 6.8	−26.9 ± 6.1	−24.9 ± 7.9				
	1	−25.3 ± 4.7	−24.4 ± 5.2	−28.2 ± 6.5	−25.0 ± 2.7				
	3	−26.4 ± 6.0	−28.3 ± 6.7	−26.8 ± 8.4	−24.9 ± 4.2				
Mitral E-wave deceleration time (ms)	0	178 ± 48	183 ± 31	195 ± 42	178 ± 42	0.019	0.580	0.992	0.583
	0.1	215 ± 48	196 ± 51	204 ± 71	182 ± 56				
	1	172 ± 51	187 ± 60	193 ± 61	202 ± 66				
	3	173 ± 66	165 ± 44	174 ± 63	156 ± 31				
E/e' ratio	0	6.0 ± 1.3	5.3 ± 1.3	5.7 ± 1.3	6.0 ± 1.7	<0.001	0.152	0.160	0.426
	0.1	5.3 ± 1.1	5.3 ± 1.2	5.5 ± 1.1	6.0 ± 1.5				
	1	5.3 ± 0.7	5.5 ± 1.2	5.9 ± 1.1	6.2 ± 2.1				
	3	6.2 ± 1.4	6.6 ± 1.4	6.7 ± 1.9	6.5 ± 1.8				

Data are mean ± SD. FC, fludrocortisone; HC, hydrocortisone; LV, left ventricular; PE, phenylephrine; RV, right ventricular.

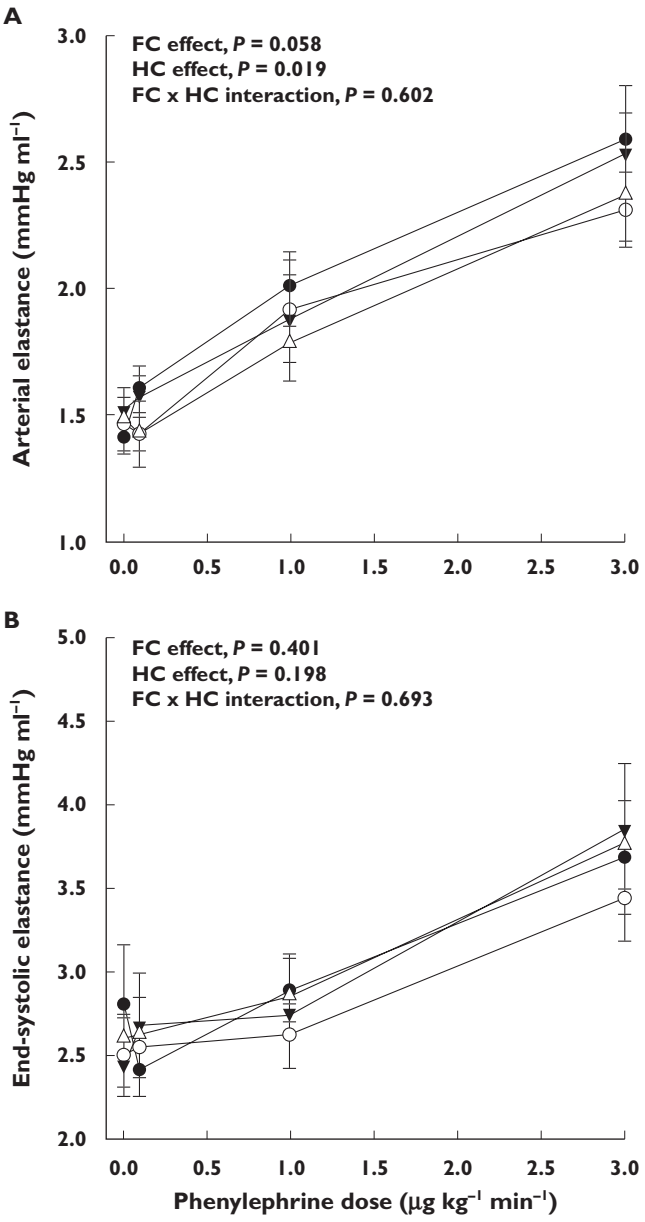

Figure 3

Variations of arterial elastance (A) and end-systolic elastance (B) induced by stepwise infusion of phenylephrine. Data are mean ± SEM; ○ FC, fludrocortisone; ▼ HC, hydrocortisone; ● placebo; △ FC + HC

Discussion

We designed this study to assess the effect of a single administration of FC and HC, alone or in combination, using the single doses of each drug that are normally administered for septic shock, in a model of hypoaldosteronism induced by acute NaCl 0.9% infusion in healthy volunteers. This model was used to mimic septic shock conditions since the benefit of steroid treatment is more marked in septic shock patients with impaired adrenal function [1, 5]. Unexpectedly, while testing the hypothesis that FC and HC could enhance the pressor response to PE, we found that the two drugs decreased this response. It is noteworthy that these effects occurred at a time where FC and HC had not induced any systemic haemodynamic effect.

The decrease of the vascular response to PE induced by steroids is probably an expression of non-genomic effects. In the literature, conflicting results have been reported concerning non-genomic effects of both mineralo and glucocorticoids. Aldosterone was shown to counteract the vasoconstriction induced by exposure to potassium in rabbit renal afferent arterioles [19], and to PE in rat aortic rings [20]. These non-genomic effects, appearing within a few minutes following the exposure to aldosterone, were attributed to an endothelium-dependent mechanism which involved the activation of endothelial nitric oxide (NO) synthase by a phosphatidylinositol 3-kinase pathway. In healthy volunteers, intra-arterial infusion of aldosterone produced a decrease [13], an increase [21] or had no effect [22], on forearm blood flow assessed by venous occlusion plethysmography, within minutes after infusion. Since both constrictive and relaxing effects have been observed, it has been proposed that under certain conditions, such as a low level of oxidative stress, aldosterone may promote NO production and vasodilatation, while in situations with increased oxidative stress and endothelial dysfunction, it could cause vasoconstriction [23]. Concerning glucocorticoids, dexamethasone has been shown to stimulate endothelial NO synthase in human endothelial cells [24], and to decrease the contraction induced by PE in rat aortic rings through the activation of endothelial NO synthase [25], whereas HC has been shown to increase dose-dependently PE-mediated constriction in rat aortic rings [20]. In humans, a single intravenous injection of HC was able to improve vascular responsiveness to norepinephrine [5] and PE [6] 1 h after injection, both in healthy volunteers and in septic shock patients. It therefore appears that both glucocorticoids and mineralocorticoids could have non-transcriptional constrictive and relaxing effects and that vasodilatation is mediated by an endothelium-dependent mechanism involving the activation of endothelial NO synthase and the production of NO [26].

Our results contrast with those observed in healthy volunteers in our two previous studies which explored the effects of HC on vascular responsiveness to catecholamines [5, 6]. The main difference between present and previous protocols was the acute NaCl 0.9% infusion performed just before treatment administration. This volume expansion, approximately equivalent to one-third of the total blood volume, induced strong modifications in terms of systemic haemodynamics and response to PE infusion. For instance, under placebo conditions, mean systolic, diastolic and mean blood pressures were 122, 71 and 88 mmHg, respectively, after volume expansion [14] and 113, 55 and 73 mmHg, respectively, without volume

expansion [6]. Moreover, under placebo conditions, at a dose of PE of 3 μg kg^{-1} min^{-1}, the mean increase of mean blood pressure was 55 mmHg in the current study whereas it was about four times lower without volume expansion [6]. It can therefore be hypothesized that volume loading modified arterial compliance (i.e. the slope of the relationship between arterial volume and arterial pressure). This could explain why the tolerance to the stepwise infusion of PE was lower in the current than in our previous study [6], preventing reaching the maximum dose of 12 μg kg^{-1} min^{-1} initially planned in the protocol. The observed decrease in the pressor response to PE induced early by steroids was accompanied by a decrease in arterial elastance suggesting that fluid loading could be another mechanism promoting the vasodilating effects of steroids in non-stressed organisms through a non-genomic mechanism. This effect is not in contradiction with the fact that steroids could enhance vascular reactivity to vasoactive agents in septic shock, as shown with HC [5, 6]. Indeed, even if septic shock patients receive large amounts of fluid in addition to catecholamine treatment, they are also in pathological conditions characterized by a high level of oxidative stress and endothelial dysfunction which are both supposed to promote the non-genomic vasoconstrictive effect of steroids [23].

Finally, echocardiographic measurements confirmed that the effect induced by FC and HC on PE dose–pressor response relationship resulted from a pure vascular action of the two drugs. Indeed, none of the components of LV systolic deformations studied was affected by FC or HC. In addition, end-systolic elastance and RV longitudinal function, as well as LV relaxation or loading conditions as assessed by the E/e' ratio, were unchanged. Thus, it was not surprising that, although not significant, the effects of steroids on the increase of systemic vascular resistance induced by PE paralleled the effects of steroids on the increase of mean blood pressure induced by PE.

Our experimental conditions constitute a limitation of our study since our model has several important differences with real life septic shock. First, the volunteers were not subjected to an infectious process and did not display a shocked state. Second, even if hypo-aldosteronism was observed, it was also accompanied by a decrease in plasma renin concentration. In septic shock patients, increased plasma renin activity is frequently observed leading to an hyper-reninaemic hypo aldosteronism which is related to the severity of the patients [27]. This underlines the need to investigate further the comparative vascular effects of hydrocortisone and fludrocortisone in septic shock patients.

In conclusion, we showed that single administrations of FC and HC decreased the pressor response to PE in healthy subjects after acute volume loading and these effects were additive. These similar effects of HC and FC probably express a rapid non-genomic vasodilating effect of steroids in the context of acute volume loading. Further studies are required in patients with severe sepsis and septic shock with different fluid infusion conditions to investigate further this issue.

Competing Interests

There are no competing interests to declare.

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